## REMARKS

### 1. Status of the claims

Currently amended claims 1, 6, 8, 19, and 20, and claims 2-5, 7, 9-14, and 21 are pending in the application. All claim amendments are supported by the specification as originally filed and thus do not constitute new matter.

### 2. Nucleotide Disclosure pursuant to 37 CFR § 1.821(a) and (d)

The Applicants have amended the specification and respectfully submit that the specification fully complies with the provisions of 37 CFR § 1.821(a) and (d). The Applicants hereby submit a substitute computer readable copy and paper copy of the Sequence Listing and respectfully request the substitute copy of Sequence Listing be inserted into the application.

The content of the paper and computer readable copies of the Sequence Listing are the same and neither contains new matter.

### 3. Specification

The Examiner objected to the specification for referring to figures 1-11. The Applicants have amended the specification to delete any reference to figures and respectfully submit that the amendments obviate the objection.

### 4. Claim rejection under 35 USC § 101

The Examiner rejected claim 19 based on the assertion that the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process. The Applicants respectfully traverse the rejection.

Original claim 19 was directed to an immunization composition and not a use or process. Thus, it is not required to set forth any steps. However, in order to expedite prosecution the Applicants have amended the claim and respectfully submit that the amendment obviates the rejection.

### 5. Claim rejection under 35 USC § 112, second paragraph

The Examiner rejected claims 6, 7, and 19 under 35 USC § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.



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Specifically, the Examiner rejected (a) claims 6 and 7, alleging that there is only one $N_3$ nucleotide and thus "other $N_3$ nucleotide" do not exist; and (b) claim 19, alleging that the claim fails to set forth any steps involved in the process. The Applicants respectfully traverse the rejection.

In order to expedite prosecution of the application, however, the Applicants have nonetheless amended claims 6 and 19 without prejudice to their future filing in a separate application. The Applicants respectfully submit that the amendments obviate the rejections of claims 6, dependent claim 7, and claim 19.

## 6. Claim rejection under 35 USC § 112, first paragraph

Claims 20 and 21 stand rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The assertion was made with reference to Parronchi *et al.* (Journal of Immunology, 1999 Vol. 163:5946-5953), Singh *et al.* (Nature Biotechnology, 1999 Vol. 17:1075-1081), Brach *et al.* (TIBS, Feb. 1998, Vol. 23:45-50), Jen *et al.* (Stem Cells, 2000 Vol. 18:307-319), and Dias *et al.* (European Journal of Pharmaceutics and Biopharmaceutics, 2002 Vol. 54:263-269)

Specifically, the Examiner asserted that the nature of immunostimulatory sequences active in humans remains unclear based on teachings of Parronchi *et al.* and that immunostimulatory oligonucleotides were mainly tested in rodent model and with murine cells whereas the effects of immunostimulant oligonucleotides in humans remains to be established based on the teachings of Singh *et al.* The Examiner further alleged that nucleic acid therapy in general is unpredictable in view of antisense technology-based therapy discussed in Branch *et al.*, Jen *et al.*, and Dias *et al.* The Applicants respectfully traverse the rejection.

In support of the rejection, the Examiner cited examples in antisense technology as a basis for claiming lack of predictability in the use of immunostimulant oligonucleotide. The application of the results from the antisense art to the issue of enablement of claims 20 and 21 is inappropriate. Antisense studies and immunostimulatory studies observe different effects induced by different mechanisms, and the Examiner has provided no link between the results obtained from antisense therapies and those obtained in immunostimulatory studies. Accordingly, the antisense art used to support this enablement rejection is simply inapposite.



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In addition, the art demonstrates that there is a correlation between observation of B cell activation by immunostimulatory oligonucleotides *in vitro* and *in vivo* results. Included herewith are copies of two publications showing a correlation between *in vitro* and *in vivo* activity. Davis *et al.*, *J. Immuno.* **160**, 870 (1998), teaches in the paragraph bridging the two columns on page 873 that measurements of B cell activation *in vivo* by immunostimulatory oligonucleotides containing the CpG motif are consistent with *in vitro* results. And Hartmann *et al.*, *J. Immuno.* **164**, 1617 (2000), reported that B cell activation *in vitro* is a good predictor for *in vivo* adjuvant activity of immunostimulatory oligonucleotides. Examples 3 and 6 of the present specification both report that the claimed immunostimulatory oligonucleotides of the present invention activate B cells *in vitro*, and, therefore, based on Davis *et al.* and Hartman *et al.*, one of ordinary skill in the art would reasonably expect the presently claimed oligonucleotides to be immunostimulatory *in vivo* as well.

Furthermore, the Examiner asserted that the specification does not provide guidance for the delivery of immunostimulant oligonucleotide into the target organs or cells in a human in an amount sufficient to stimulate an immune response. The Applicants respectfully contend that the specification does provide guidance for using immunostimulant oligonucleotides in an immunization composition, for example, on page 9, line 14 to page 10, line 29. Furthermore, methods for administration and delivery of an immunostimulant oligonucleotide into a human in a sufficient amount to stimulate immune response is already available to the public at the time of filing, for instance, as described in US patent No. 5,663,153 (examples 9-12), and WO 98/52962 (example 11), both of which are specifically cited in the specification. "The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." MPEP § 2164.05(a) citing In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)) The Applicants thus respectfully submit that the specification enables one of skilled in the art to make and use the claimed invention without undue experimentation.

In summary, the Applicants respectfully submit that claims 20 and 21, when read in light of the specification, enable one of skill in the art to make and use the claimed invention. The Applicants thus respectfully request withdrawal of the rejection on this ground.



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**7. Claim rejection under 35 USC § 102**

a. The Examiner rejected claims 1, 2, 9, 10 and 19 under 35 USC § 102(b) as being anticipated by Hutcherson *et al.* (WO 95/26204).

Specifically, the Examiner asserted that Hutcherson *et al.* disclose an immunostimulant oligonucleotide (SEQ ID NO:1, TTGCTTCCATCTTCCTCGTC) comprising the formula 5' $TTN_1N_2TT$ 3' of the current invention. The Applicants respectfully traverse the rejection.

Currently pending claim 1 excludes oligonucleotides having a dinucleotide CG in which the cytosine C is not methylated.

SEQ ID NO:1 of Hutcherson *et al.* contains a dinucleotide CG in which the cytosine C is not methylated (nucleotide numbers 17 and 18). Therefore, Hutcherson *et al.* do not anticipate claim 1, or dependent claims 2, 9, 10, and 19. The Applicants thus respectfully request withdrawal of the rejection on this ground.

b. The Examiner rejected claims 1, 2, 9, 10 and 12 under 35 USC § 102(b) as being anticipated by Parronchi *et al.* (Journal of Immunology, 1999 Vol. 163:5946-5953)

The Applicants respectfully submit that the cited reference was published in the December 1999 issue of Journal of Immunology, which is after the priority date of the instant application (June 8, 1999). Thus, Parronchi *et al.* is not prior art against the instant application. The Applicants herewith submit a copy of table of contents of the December issue of Journal of Immunology for the Examiner's review and respectfully request withdrawal of the rejection on this ground.

c. The Examiner rejected claims 1-8, 9, 13, 14 and 19 under 35 USC § 102(b) as being anticipated by Liang *et al.* (Journal of Clinical Investigation, 1996 Vol. 98:1119-1129)

The Examiner asserted that Liang *et al.* disclose phosphorothioate oligodeoxyribonucleotides, including oligonucleotide 2105: 5'- TTGCTTCCATCTTCCTCGTC-3', DSP19 5'-NNNNNNNNNNNNNNNNNNN-3', wherein N is A, T, C, of G, DSP28: 5'-TTTTTTTTTTTTTTTTTTT-3', DSP39: 5'-TTTTTTTT-3', and DSP40: 5'-TTTTTTTTT-3', some of which allegedly activate human B cell. The Examiner asserted that the above-mentioned oligonucleotides anticipate claims 1-8, 9, 13, 14 and 19 of the instant application. The Applicants respectfully traverse the rejection.



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Oligonucleotide 2105 contains a dinucleotide CG in which the cytosine C is not methylated (nucleotide numbers 17 and 18). In addition, Liang *et al.* specifically teaches that unmethylated CpG motif is important in inducing maximal sODN-induced activation of human B cells. Page 1126, right column, third paragraph. As stated in the argument set forth in subsection (a) above, oligonucleotide 2105 does not anticipate claim 1 or any dependent claims thereon of the instant application.

Currently amended claim 1 recites, "$N_1$ and $N_2$ are each independently represent adenine, thymine, cytosine or guanine, in which $N_1$ and $N_2$ are not both thymines." Thus, oligonucleotides DSP28, DSP39 and DSP40 do not anticipate claim 1 or any dependent claims thereon.

DSP19 defines a genus of oligonucleotides. A genus does not anticipate a species unless the genus clearly names the claimed species or one of ordinary skill in the art can "at once envisage" the species within the genus. MPEP § 2131.02. Liang *et al.* fails to name the presently claimed oligonucleotides or provide any teachings that would enable one of ordinary skill in the art to "at once envisage" the presently claimed oligonucleotides. In fact, Liang *et al.* teaches that DSP19 represents a completely random sequence of 20 deoxyribonucleotide with no sequence preference. Therefore, the Applicants submit that Liang *et al.* cannot anticipate the present claims and respectfully request withdrawal of this rejection.

d. The Examiner rejected claims 1-3 under 35 USC § 102(b) as being anticipated by Lang *et al.* (European Journal of Immunology, 1999 Vol. 29:3496-3506)

The Applicants respectfully submit that the cited reference was first published online on October 25, 1999, and later published in the November 1999 issue of European Journal of Immunology, neither predates the effective filing date of the instant application (June 8, 1999). Thus, Lang *et al.* is not prior art against the instant application under 35 USC § 102(b). The Applicants herewith submit a copy of table of contents of the November issue of European Journal of Immunology for the Examiner's review and respectfully request withdrawal of the rejection on this ground.



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## 8. Conclusion

In view of the foregoing, it is believed that all requirements of patentability are fully met and, accordingly, allowance of the claims is respectfully requested. If the Examiner believes it to be helpful, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

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